System for Recording Evoked Potentials in Liquid Biological Matrix

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***Abstract*— The article deals with the development and investigation of a system for recording, amplifying and processing weak evoked potentials in liquid biological matrix. The main attention is paid to the study of the parameters of this system.**

Keywords*— *biopotential; piezobiosynthesis; amplification system; transfer characteristic; signal-to-noise ratio.

I. INTRODUCTION

The study of weak energy transformations in cellular structures and individual cells is actively conducted in recent decades. The first studies of biopiezoelectrics were made in 1963: Shamo and Lavin discovered piezoelectric effect in bones [1]. Later they postulated piezoelectricity on the fundamental property of biological materials.

Subsequently, the piezoelectric effect was detected at a macroscopic level in both hard tissues (teeth, horns, cartilage) and in soft tissues (pineal gland - S. Lang et al., 1996) [2], as well as at micro- and nanoscopic (bones - C. Halperin et al., 2004) [3] and molecular (amino acids) levels.

Measurements of spontaneous polarization and hysteresis loop are the most direct method for determining the presence of ferroelectrics, especially in organic materials. In this case the absolute value of the spontaneous polarization was measured for a large number of organic ferroelectrics (S. Horiuchi, Y. Tokura, 2008 - ref. 49 [4]).

V.C. Yarmarin et al. (2009) [5] conducted a detailed analysis of experimental data on the investigation of dielectric characteristics of DNA. It was shown that the anomalously high value of dielectric permittivity obtained earlier for DNA samples, as well as the presence of dielectric hysteresis loops, are due not to ferroelectric properties, but to a redistribution of the measured voltage across the thickness of the samples.

V.V. Lemanov et al. (2011) [6] considered a hypothetical phase transition of D2-C2 in protein amino acids using the concept of ferroics (Aizu et al.).

Known for more than 30 years, piezoelectric effects in biological tissues have been studied only at the level of macrostructures, although they are used to obtain additional diagnostic information, irrespective of chemical and biological changes in living biological tissues.

II. ORIGINS OF THE IDEA

In 2013, a group of Kharkiv scientists discovered the phenomenon of piezobiosynthesis [7].

The phenomenon of piezobiosynthesis is the emergence of potentials in the object under investigation (a biological cell, a tissue site) with a change in the pressure applied to it. In modern medicine, various factor influences on biological tissues are widely used: thermal, chemical, mechanical, etc. However, effects of the emergence of evoked potentials in biological tissues, known for more than 30 years, have been studied only at the level of macrostructures and are used to obtain some specific effects (regenerative medicine).

Existing theoretical developments are limited to the framework of general biological models of metabolic processes in living multicellular structures, without specifying modifications of such models at the level of single cells. Moreover, practically no theory has been developed and no technical means of monitoring, diagnostics, identification of the level of biological activity and vital activity of living cells have been created, allowing to identify mechanically induced electrophysical effects in cells, which would help to obtain additional information on trends in dynamic electrochemical processes characterizing the degree of metabolism and the vital activity of living cells. Such information would undoubtedly increase the probability of decision-making, not only in existing information diagnostic systems, but would also open up new opportunities for creating methods and technical means for predicting and early diagnosing pathological changes at the level of both single cells and biological structures which, in turn, will increase the level of medical assistance to the population.

To implement such a system at the hardware level, it is necessary to ensure the normalized pressure applied to the samples under study, as well as the accuracy of processing the data obtained at all stages of the measurement.

III. MATHEMATICAL JUSTIFICATION

In early 2015, a series of experiments was carried out, the purpose of which was to confirm the presence of a piezoelectric effect in liquid biological samples. For this, the objects of three states were taken: S_0- physiological saline, S_1 - whole blood without pathology, S_2 - whole blood with oncopathology (colorectal cancer).

For these objects, an analysis of the dynamic features of the induced electro-potential processes was made. The registration of the electric voltage U(t) on the electrodes of the electro-potential measuring transducer showed practically complete identity of the process of atmospheric "loading-unloading" P(t) to the process U(t).

Taking into account that U(t) changes nonlinearly at other time intervals, we can assume the existence of an additive model of the dynamic electro-potential interaction for the observed process U(t).

$$U(t) = E(t) + e(t), \quad (1)$$

where E(t) is the process of change in the total electrical potential of the liquid biochemical sample induced by the factor load (total EMF, proportional to the change in the load P(t), e(t) is the quasi-permanent internal EMF of molecules (cells) of the liquid sample, changing stepwise and in antiphase with E(t) its levels, providing U(t) for the observed process.

If we consider the velocity $V_e(t)$ as the first derivative of the process $e(t)$ in time, then multiplying the right-hand side of the expression by

$$\frac{dV_{\mathrm{U}}(t)}{dV_{\mathrm{U}}(t)} = 1, \quad (2)$$

and combining the elements of the factors, we obtain, to the right of the equality sign, new factors, the first of which characterizes the rate of change of the potential $e(t)$ in the function of the velocity $V_U(t)$, and the second factor is the acceleration of the process $U(t)$

$$V_e(t) = \frac{de(t)}{dV_{\mathrm{U}}(t)} \cdot \frac{dV_{\mathrm{U}}(t)}{dt} \quad (3)$$

Information on the biochemical state of the sample is also carried by the parameters of the impulse change in the velocity $V_e(t)$ of the electric potential $e(t)$.

For the research, the parameters Y_1, Y_2 and Y_3 were chosen based on the geometry of the derived derivatives $V_U(t)$ [8], characterizing the dynamic differences of the whole blood sample without pathology and a blood sample with oncology.

Statistical estimation of the effect of the state of the object on the character of the electric potential response $U(t)$ under the influence of the acting factor $P(t)$ was carried out on the basis of F - statistics,

$$\mathrm{F}_{1;8} = \left(\frac{N \cdot \sum_{j=1}^{K} (\bar{Y}_j - \bar{Y})^2}{\sum_{j=1}^{K} \sum_{i=1}^{N} (U_{ji} - \bar{Y}_j)^2} \right) \cdot \left(N_{\Sigma} - K \right), \quad (4)$$

which values for the parameters Y_0, Y_1, Y_2, are 6,101; 10,28; 8,22, respectively, under critical statistics.

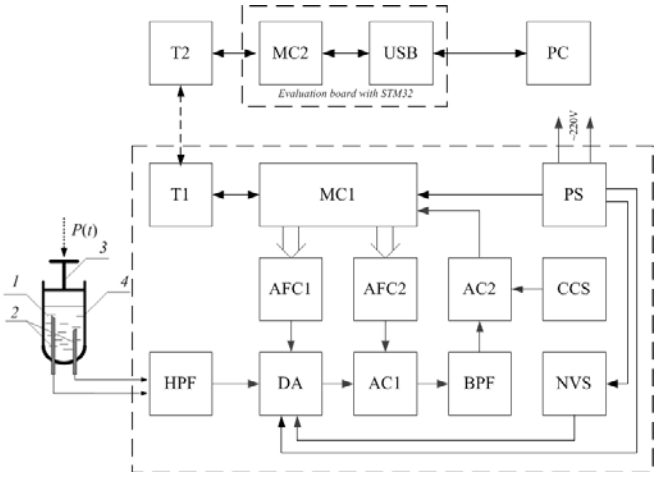
This means that any of the parameters Y_1, Y_2, or Y_3, allows to detect with 95% significance the change in the state of the controlled biological sample.

IV. Goal of the Research

The goal of the research is to develop and study a system that will allow recording of evoked potentials in liquid biological matrix.

V. Description of the Device

The Department of Industrial and Biomedical Electronics developed and implemented a system for recording evoked potentials in liquid biological matrix. The structural diagram of the system is shown in Fig.1. The appearance of the primary converter is presented in Fig. 2.



1 – liquid sample; 2 - gold-plated electrodes of different lengths; 3 - movable piston; 4 - cylindrical chamber

Fig. 1 – Structural diagram of the system of registration of evoked potentials in liquid biological matrix

In this scheme, the measuring signal of the research object is fed through the electrodes to a high-pass filter (HPF) to eliminate a constant component of the signal, which, with further amplification, will interfere measuring of the signal. After filtering, the signal is fed to a differential amplifier (DA), which is powered by a bipolar voltage. To obtain the required supply voltage, a negative voltage source (NVS) is used, which allows the differential power supply to the amplifier. To obtain the necessary amplification of the signal, an amplification factor controller (AFC1) is used, which is controlled by a microcontroller (MC1). Since the amplification after the differential amplifier may not be sufficient, the signal is then fed to the amplifying cascade (AC1), whose amplification factor is also set by the amplification factor controller (AFC2). To eliminate interference, a bandpass filter (BPF) is used. For the final amplification of the signal to the required level, the last amplifying cascade (AC2) is used, after which the signal is fed to the analog-to-digital converter of the microcontroller. A constant component source (CCS) provides a signal bias for half the supply voltage of the microcontroller

so that it can get its entire dynamic range. From (MC1), the signal is fed to the transceiver 1 (T1). By wireless communication, it transmits the processed information to the transceiver 2 (T2), which is connected to a debugging stand based on a microcontroller (MC2). After that (MC2) forms data packets in order to transfer them using the interface (USB) to a personal computer (PC) in the required format for further display. The system is controlled with the help of (PC) through the program "Oscil", designed to work with the stand. The image of the working area of the program is shown in Fig. 2.

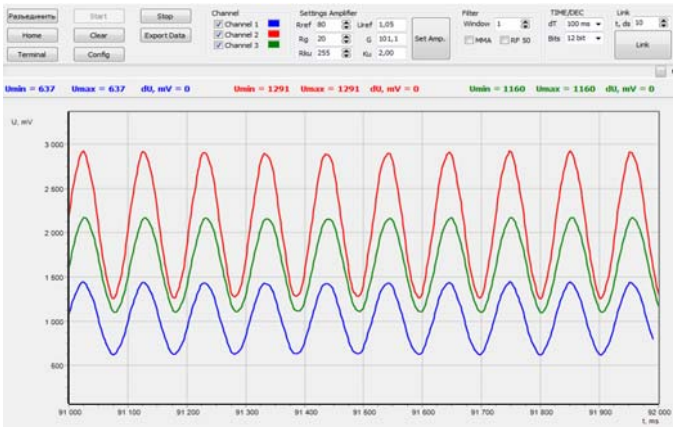


Fig. 2 –Working area of the program «Biopotential»

The program "Oscil" allows you to control the amplifying cascades of the measurement system from a PC and display the data obtained after processing by the microcontroller. The main functionality is:

- setting the amplifier factor of the first amplifying cascade;
- setting the amplifier factor of the second amplifying cascade;
- setting the offset level for the first amplifying cascade.

The range of these values varies from 0 to 255 numeric code. In this case, the program displays the actual amplification factors of the cascades, in accordance with the selected numerical code.

There is the possibility of displaying both the channels of the amplifier system, and each one separately with the display of the minimum and maximum voltage values, and, also, the difference of these values. In the program there is the possibility of activating digital filters: a 50-Hz rejector filter and a moving average filter with a different window.

It is also possible to save the received data in various formats, such as .txt, .xlsx, .jpg, etc.

VI. RESEARCH

According to the results of experimental studies, it was found that the signals studied have the following parameters:

- the constant component of the signal is 40 mV;
- the useful amplitude of the signal is 6 mV;
- the frequency of the useful signal is 0,3-10 Hz.

To register signals with such parameters, appropriate technical tools and software were developed.

However, the effectiveness of such studies is provided not only by software and hardware, but also by statistically based planning of the experiment, the choice of information indicators of a measuring signal with a high level of informativeness.

During the pilot studies, the following parameters were studied:

– the transfer characteristic of amplifying cascades;

– amplitude-frequency response of amplifying cascades;

– investigation of the intrinsic interference of amplifying cascades.

1. For experimental study of the dependence of the established amplifying factor on the measured amplifying factor on the input of the investigated scheme, voltage was supplied from the generator controlled by a millivoltmeter from 5 to 30 mV. By changing the amplification factor, a digital oscilloscope fixed the output voltage. Based on the obtained data, the dependence of the output signal on the voltage at the input of the system was constructed, Fig.3. Then, we calculated the real amplification factor by formula.

$$K_{U_{вх}\ exp.} = \frac{U_{вих}}{U_{вх}}, \qquad (5)$$

To calculate the error of the real amplification factor from the established, a calculation was made by the formula.

$$\delta, \% = \frac{|K_{u\ exp.} - K_{u\ calc.}|}{K_{u\ calc.}} \cdot 100. \qquad (6)$$

The values of the error of the amplification factors from the calculated value are shown in Fig. 4.

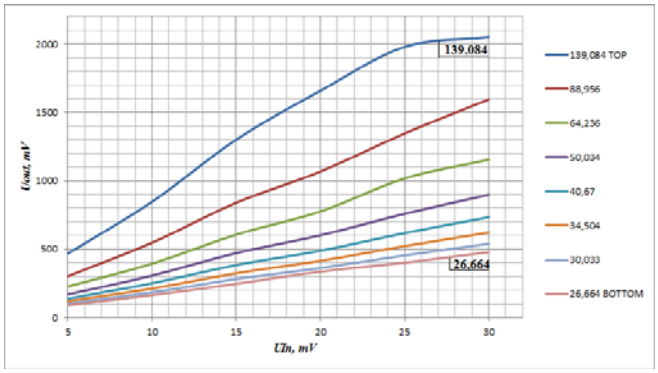


Fig. 3 - Graph of the dependence of the output signal on the input voltage for different amplification factors

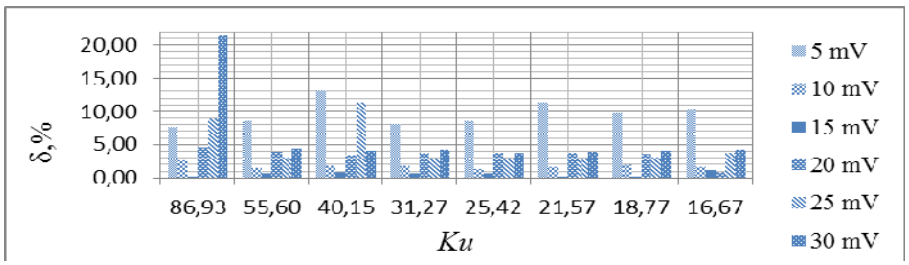


Fig. 4 - Graph of the dependence of the measurement error for different valuesof the amplification factors

2. Investigation of amplitude-frequency response was carried out as follows: a sinusoidal signal of a fixed amplitude with a frequency of 0.01 to 600 Hz was sent from the generator to the input of the system at various amplification factors. According to the research, graphs of the dependence of the transmission factor (the ratio of the amplitude of the output signal to the amplitude of the input signal) as a function of frequency were plotted. The amplitude-frequency response is shown in Fig.5.

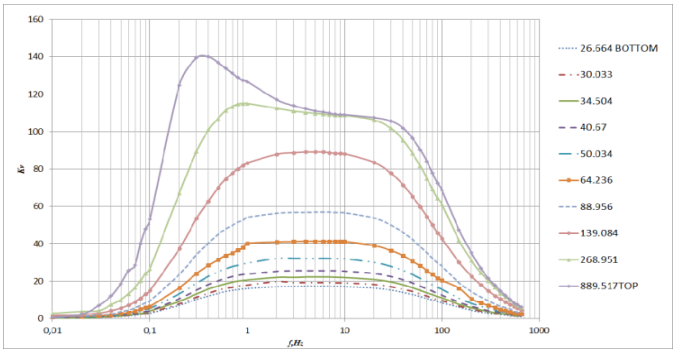


Fig. 5 – Amplitude-frequency response of systems

From the obtained data it follows that the cutoff frequencies of this system are at the level of 0.3 Hz for the lower cutoff frequency and 60 Hz for the upper frequency.

3. One of the tasks in testing the system was to investigate interference when using various electrical power options of the system. The following variants were implemented:

a) using the USB power of the computer port;

b) using of an external transformer power supply.

In both cases, to determine the level of interference present in the output signal, the system input signal contact was connected to the ground to provide zero potential and to measure the intrinsic noise of the amplifier cascades, or was left unconnected. During these experiments, connection between the debugging modules was carried out using a wireless connection.

Based on the data obtained as a result of the system study, the signal-to-noise ratio was calculated using the formula.

$$SNR = 10\lg\frac{P_{sig}}{P_{n}}. \qquad (7)$$

Based on the results of these calculations, it is determined that the level of interference in the output signal when using an external transformer power supply is much lower than when using the USB port of the computer. The results of the calculations are given in Table 1.

TABLE I. THE RESULTS OF SIGNAL/NOISE RATIO CALCULATIONS

AMPLIFICATION FACTOR	POWER SUPPLY UNIT		*USB*	
	GND	*w\o input*	*GND*	*w\o*
26	55,03812	41,16855	36,38891	40,3874
270	48,16023	32,19652	25,3984	30,6624
13448	38,56984	16,5784	9,923922	5,33882

VII. CONCLUSION

Based on the results of the research, a prototype of the system for recording evoked potentials using an external transformer power supply was developed and implemented. The study found that the system bandwidth is 59.7 Hz from 0.3 to 60 Hz, the error in setting the amplification factors for almost the entire range of input signals does not exceed 10%, and the signal-to-noise ratio ranges from 48 to 32 dB. Further improvement of this system will allow to obtain more accurate information about the state of biological matrix, which, in turn, will favorably influence the development of the theory of piezobiosynthesis and will allow to get new diagnostic information.

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